AMINO ACIDS AND HYPERTENSION*

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The metabolism of matter and the formation of wastes, are normally supported by the food, but if no food is taken, these processes still continue at the expense of the body substance. The expenditure of energy, which is never ceasing in the living body, includes the work involved in carrying on the internal processes which are essential to life itself, and the expenditure of matter cannot cease, as the energy for this necessary work is obtained by the breaking down of organic compounds of the food, or of the body into simpler compounds, some of which are of no further use and must be eliminated, while others form the building materials from which the body structure is renewed. When the food supplies sufficient energy, the body substance is protected. When the food is insufficient, body substance is burned as fuel. Therefore, we must know whether the fuel requirements of the body have been fully met before we can intelligently consider its nutritive requirements. Carbohydrates, fats, and proteins all furnish fuel, but protcins alone serve for maintenance and growth of body tissue. However, as amino acids are what the body needs and not proteins as such, there must be a definite amount of that class of proteins which contain all the amino acids, since the human body cannot synthesize them, and a lack of either may make it impossible for the organism to manufacture its own tissue protein, and in consequence it suffers a kind of starvation.

Nutrition has been studied from different angles and by many different methods, and still there is much to be learned. The method which at present is engaging the most attention is that which seeks to follow the chemical composition of food in its course through the animal organism. This includes a biochemical analysis of the component parts of the various foods, especially of the proteins.

Until within the present century all proteins were regarded alike in dietary value, and Liebig, Voit, Pflüger, and Rubner in turn advanced their views of protein metabolism, all of which were finally disproved by Folin and others,[1] who also demonstrated the fact that protein disintegration was accomplished in the digestive tract by a series of hydrolytic splittings, and that nitrogenous nutritional requirements could be supplied by a mixture consisting of the products of hydrolysis of the protein molecule. Dogs were fed on the products of the self-digestion of the pancreas, and on this diet, which contained not a trace of protein, body weight was maintained. It has since been demonstrated that life can be supported upon a diet consisting of a suitable mixture of amino acids.[2] A boy with an esophogeal stricture, on whom gastrotomy had been performed, was fed per rectum on the digestive products of meat, obtained through the combined action of trypsin and erepsin. Not only was nitrogen equilibrium maintained, but the body weight increased. Such experiments, Underhill[3] claims to be conclusive evidence, that we must regard the amino acids as food stuffs which are sufficient for the nitrogenous needs of the body and that the nutritive value of any protein is dependent upon the content and character of its amino acids.

The protein molecule is digested by the action of pepsin, trypsin, and erepsin down to amino acids in the digestive tract. This action, however, is a gradual one and more in the nature of a slow erosion than that of a rapid explosion. There are eighteen individually distinct amino acids which, though they resemble one another structurally, cannot substitute each other. Chemically, they are organic acids in which one or two atoms of hydrogen have been replaced by the amino group NH_2. According to Van Slyke,[4] the most striking characteristic, which is common to all amino acids, is the occurrence in the same molecule of an amino group with the basicity like that of ammonia, and an acid group with an acidity like that of acetic acid (hence the name amino-acid). He likens the entire protein molecule which is a chain of amino acids to a long train of automobiles all with the same black uniform bodies, but with tops of eighteen different shapes, and of three different colors, according to whether their properties are acid base or neutral. Chemically stated, the complete digestion of a protein molecule consists in splitting or breaking this long chain into shorter chains, the albumoses, then into still shorter chains, the peptones and peptids, and finally the individual amino acids of which it is composed. Until within the past five years, nothing was known of the fate of the amino acids after they left the intestinal tract. At that time, Van Slyke states, the mechanism of protein nutrition stopped short against the intestinal wall. Folin and Van Slyke[5] later proved beyond question that amino acids were normally absorbed directly into the blood from the intestines, and from the blood distributed to the tissues without further chemical change, those not needed for synthesis being changed by a process of diamination into ammonia and urea, the carbonaceous residue being transformed into carbohydrates, yielding energy. The tissues absorb amino acids rapidly, but never completely. The blood, normally, always contains about 0.1%, while the tissues contain ten times this amount. The free amino acids stored in the

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1. Folin: American Journal of Physiology, 1905, 13, p. 45.
2. Abderhalden: Zeitschrift fur physiologische Chemie, 1912, 77, p. 22.
3. Underhill: The Physiology of the Amino Acids, 1915: Yale University Press.
4. Van Slyke: Donald Archives Internal Medicine.
5. Folin & Van Slyke: Journal A. M. A., 1914, 63, p. 823.

tissues may be regarded as a form of reserve food. This reserve, however, does not disappear during long fasting. On the other hand, they tend to increase during starvation.[6] These facts are believed to indicate[7] that the amino acids are intermediate steps, not only in the synthesis, but in the breaking down of body proteins, and that autolysis is the main source of free amino acids found in the fasting body.

The urea formation while taking place in every tissue of the body is accomplished mainly in the liver. That organ is the principal factor in absorbing amino acids from the blood stream and also in the chemical transformation which precedes the elimination of urea. Van Slyke and Meyer state, that the liver, also, constantly desaturates itself by metabolizing the amino acids that it has absorbed, and thus maintains indefinitely its power to continue removing them from the circulation, so long as they do not enter it faster than the liver can metabolize them. If they enter too rapidly, or if the liver function is lowered, the amino acids increase in the bood, and the kidneys assist by excreting them unchanged. An excess, therefore, of amino acids in either blood or urine, might indicate a lowered function of the liver. Indeed amino acids have been given as a test for functional activity of the liver. It has also been stated, that mild cases of diabetes, while lacking the ability to oxidize glucose, still possess the power to change amino acids to glucose, and that a lack of this ability might be taken as an indication of lowered liver function. All of these results tend to change our older theories of metabol ism as Underhill observes, and it becomes evident, that in any consideration of protein transformation within the organism, either in health or disease, amino acids are the substances which demand attention. Moreover, he adds, that at present the investigations are being narrowed down to the point of the determination of what actually occurs with the individual amino acids and what special role in the body nutrition, each one plays.

The defective proteins which are incapable of supporting life or promoting growth, are found to be lacking in one or more of the amino acids. It has been recently shown[8] that physiologically active substances are formed from amino acids, and if the main nitrogenous element in the diet is one of the defective proteins, there may be an imperfect functioning through failure to supply the raw materials needed by certain glands to elaborate their specific products. The normally functioning thyroid gland contains an iodine compound, which is believed to be formed from tryptophane. Therefore, if the protein in the diet contains no tryptophane, a corresponding disturbance of this gland may result. Adrenaline, a physiologically active substance, is probably derived from tyrosine and a continued lack of this amino acid in the diet would indirectly lower the function of the adrenals, resulting in certain abnormal symptoms, but differing from those of starvation. The pituitary gland also manufactures a physiologically active substance which is derived from the amino acid, histodine.

As before stated, the cleavage of the protein molecule occurs in the digestive tract, by the activity of the enzymes normally formed there. This cleavage, in general, resembles the products of putrefaction caused by the activity of bacteria. Bacterial activity, however, causes a different type of products; the specific substances formed are chemically different, and of necessity occur in different parts of the intestinal tract, since it has been found that little or no putrefaction takes place in the small intestine, and that practically no proteoses or peptones are ever found to pass the ileo-caecal valve. It would therefore seem that amino acids, principally, are concerned in the putrefactive processes in the intestinal tract, and, moreover, that this putrefaction occurs in the large intestine only. We are familiar with the putrefactive products of the aromatic amino acids, tyrosine and tryptophane, which are first deaminized, then further torn to pieces by the activity of bacteria to form the familiar substances, indole, skatole, phenol, and the oxyacids. The chemical reactions are the same with each of these amino acids, first ammonia is split off, then carbon dioxide, and finally oxidation and demethylation takes place, but from tryptophane, we have as a result, the malodorous bodies, indole and skatole, while from tyrosine are formed phenol, paracresol, and the oxyacids. These products are easily detected and as a rule are a fairly good index of the extent of intestinal putrefaction, but they are only a small portion of the substances which may be actually formed and absorbed from the intestinal tract. Indeed with no detectable indole or phenol, there may be formed from tryptophane and typrosine extremely toxic substances which are also characteristic of putrefaction. The splitting off of carbon dioxide by the so-called carboxylase bacteria, may occur either before or after deamidation. If it occurs before, compounds known as amines are produced, which are highly toxic and act principally upon the nervous system. These amines exert a powerful effect upon blood pressure and are believed to cause thickening of the artery walls. In 1907 Dixon and Taylor, using an alcohol extract of placenta, observed that when injected intravenously into animals, it caused a marked rise in blood pressure, and also contractions in the pregnant uterus. However, it was shown later that these symptoms did not occur, if the placenta had not first undergone putrefaction. Emerson had already isolated a similar substance from the so-called self-digestion of the pancreas, but it is now believed that this substance also was formed through bacterial agency. This particular body is known as para-oxyphenylethylamine or tyramine, and is produced from tyrosine by the liberation of CO_2. Tyramine resembles epinephrine chemically, and exerts a similar influence upon the sympathetic nervous system, though weaker in its action. It is found outside the body in a variety of cheeses, as Camembert, Roquefort, and in some American

6. Van Slyke: Archives Internal Medicine.
7. Van Slyke & Meyer: Journal of Biological Chemistry, 1912, 12, p. 399; 1913-1914, 16, p. 187, p. 213.
8. Alsberg: Lectures on Nutrition, 1916, Washington Academy of Sciences.

cheeses, and is the active principal of ergot. From leucine in a similar manner may be formed isoamylamine, while from tryptophane is produced indole ethylamine. Histamine, a very powerful toxin, is formed (by the action of putrefactive bacteria) from histidine. Its action on the nervous system produces symptoms identical with those of anaphylaxis. In like manner the diamines, cadaverine, putrescine, and tetramethyldiamine are formed respectively from lysine, arginine, and ornithine.

It becomes evident, therefore, that in a study of hypertension, we must reckon with not only the amino acids, but with the bacteria concerned in intestinal putrefaction. During the past three years in making observations on the flora in intestinal putrefaction we found that we could change the flora at will by changing the diet, and that coincidently with a continuous carbohydrate diet there was a disappearance from the urine of the absorption products of putrefaction. More recently, Kendall, of Northwestern University, has demonstrated that the intestinal flora are definitely related to the diet of the host, also that putrefaction may be retarded by a carbohydrate diet, and records some interesting facts as a result of his experiments. He reminds us that the bacillus bifidus which is obligately fermentative, requiring carbohydrates, is characteristic of the flora of nurslings, producing a constantly acid reaction. As the child becomes older and the diet includes more protein, this type of bacteria decreases and there is a remarkable increase in the colon bacilli which are facultative and can grow equally well on either protein or carbohydrate pabulum. The entire life cycle of these bacteria is carried on within the intestinal tract of its host and the metabolism of both microbe and host are similar in many respects. The products of the metabolism of normal intestinal bacteria are harmless, but according to the diet of the host, even a colon bacillus, which is a lactic acid bacillus, may play a dual personality. If it becomes necessary for a colon or a proteus bacillus to utilize proteins for energy, an enzyme is formed, the function of which is to prepare the protein product for assimilation, and in accomplishing this, certain chemical changes take place, as various substances are split off in order to find the carbohydrate residue necessary for the energy of the bacteria. If, however, utilizable carbohydrate is available for their energy, these enzymes are not formed. The chemical products of many of the pathogenic bacteria, in the presence of utilizable carbohydrates, are identical with those of the lactic acid bacilli, while these same organisms, if grown in carbohydrate-free media, form their specific highly toxic products. The protein sparing effect of carbohydrates, so well known in the metabolism of the human body, is here demonstrated in the metabolism of bacteria, and this fact is well worth our consideration, since we may thus shift the metabolism of intestinal bacteria by supplying available carbohydrates for their energy with a resulting formation of benign products.

During the past eighteen months we have made observations on a number of patients with varying degrees of hypertension. These observations, which have extended over periods of weeks or months, consisted of daily examination of feces, daily study of body metabolism, together with functional tests of liver and kidney. Some of these patients had lowered kidney function, others had lowered liver function, some had both, while still others had neither, but all responded promptly to a carbohydrate diet by a lowering of the blood pressure and a lessening of the products of putrefaction. Proteids were gradually and carefully added, but only up to the actual body requirements, always watching the effect upon the intestinal flora, providing for normal intstinal motility and keeping the carbohydrates so much in excess that they could not all be absorbed from the upper intestinal tract, thus insuring plenty of available suitable pabulum for the necessary energy of the intestinal bacteria.

At the present time lowered kidney and liver function, lowered pancreatic function, anemias and a number of other diseases are being cured by a proper adjustment of diet, and now hypertension may be alleviated or cured in like manner, simply by preventing the amino acids which have safely passed through the fires of protein metabolism, from being torn to pieces by the intestinal bacteria to furnish their necessary energy. Verily we live around the digestive tract.

A STUDY OF ONE HUNDRED AND FIFTY CASES OF HYPERTENSION.

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The subject is so extensive that we have limited our studies to the etiology and the treatment as carried out in the cases reported. It seems best here to define some of the terms or expressions which will be used throughout the paper.

Apical abscesses are spoken of only when the X-Rays have unquestionably demonstrated an abscess at the apex of the root of one or more teeth. The expression "bad teeth" refers to teeth that are crowned, or to a condition, which, from the appearance of both teeth and gums, is suggestive of root abscesses, but in which no X-Rays were taken.

The statement of a positive history means that one or both parents have died of apoplexy, uremia or heart failure. Moderate sclerosis refers to the radials, which, when empty, are palpable. Moderately severe sclerosis refers to radials which are becoming tortuous. Severe sclerosis to those becoming tortuous and beaded; while very severe designates a pipe-stem condition of the blood vessels.

By the term "nervous," we refer, first, to a group of patients with nervous temperaments who are high strung, intense, always keyed up to a high pitch, always on the go, never relaxing, whose motors always run at high speed. This group doesn't know how to play, but are Rooseveltian in that they are intense in all they do and a vacation means a change of but more strenuous work. These patients are always prompt at their appointsments, are exacting, and in business very successful. The second group compose women who are in the menopause period.

The following cases reported were a group of